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CLINICAL REVIEW

Sleep and fatigue in pediatric oncology: A review of the literature

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SUMMARY

Cancer in children has detrimental effects on sleep patterns and sleep quality, which in turn impacts on the perception of, and the ability to cope with, the emotional and physical challenges associated with both the disease and its treatment. This places an added burden on their quality of life that can last many years beyond diagnosis and treatment. In addition to the effect of the cancer itself, surgery, chemotherapy and radiotherapy can all contribute both short and long term to sleep disruption. Sleep disorders have also been associated with pain, fatigue, medication and hospitalisation in children suffering from cancer. This review will explore the relationship between childhood cancer and associated sleep disorders, in the acute stage of diagnosis, during treatment and in the years following. We will discuss the possible causes and the current treatment modalities used to treat sleep disorders in children with cancer, and in childhood cancer survivors. It has been estimated that the recent advances in treatment have improved the overall five year survival rate for all childhood cancers to over 80%, with some cancers achieving a near 100% cure rate such as early stage Wilms' tumour. Thus, recognition and appropriate treatment of associated sleep disorders is essential to optimise long term quality of life.

Introduction

Most commonly thought of as a modern disease, in fact evidence of cancer has been identified in Egyptian mummies that were dated to 3000 BC. Currently, even though the combined cancer death rate for adults has been declining in the last two decades, cancer accounts for one in four adult deaths [1] and is the second commonest cause of death in children in developed countries [2]. Whilst three out of five children with cancer will survive, they are at increased risk for psychological distress, neurocognitive dysfunction and poor health-related quality of life (QOL) [3]. Sleep plays a fundamental role in the psychological health, neurocognitive ability and QOL of healthy children; a role which is even more important in a child suffering illness, pain, anxiety and emotional distress [4]. Poor sleep patterns and sleep quality impacts on the perception of, and the ability to cope with, the emotional and physical challenges associated with childhood cancer and its treatment. To increase recognition of sleep problems associated with cancer by health professionals, a practice guideline has been published for the prevention, screening, assessment and treatment of sleep disturbances in adults with cancer in Canada [5]. However, there is no similar guideline for children with cancer, indicating that identifying and treating sleep disorders in pediatric oncology remains an area of research that is sadly lacking. This is even more apparent in the case of young children with cancer, where there is almost a complete dearth of research. This review will provide an overview of the current literature on sleep and fatigue in pediatric oncology.

Childhood cancer

Childhood cancers encompass a wide range of malignancies which are differentiated by histology, the sex, age and race of the child, and the site of origin of the cancer [6]. The most common

Abbreviations: ALL, acute lymphoblastic leukaemia; BMI, body mass index; CCSS, childhood cancer survivor study; CNS, central nervous system; EDS, excessive daytime sleepiness; MSLT, multiple sleep latency test; SDB, sleep disordered breathing; QOL, quality of life.

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cancers diagnosed during childhood overall, are leukaemia, malignancies of the brain and central nervous system, and lymphomas, accounting for 34%, 23% and 12% of all childhood cancers respectively [2] (Fig. 1). Acute lymphoblastic leukaemia (ALL) is in turn the most commonly diagnosed leukaemia with approximately 78% of leukaemia being ALL [7]. Astrocytoma is the most commonly diagnosed central nervous system (CNS) tumour, and Non-Hodgkin lymphoma the most common lymphoma, accounting for 47% and 46% of these types of cancers respectively [2]. However, the pattern of diagnoses of childhood cancers is very much age-dependent. Neuroblastomas represent 33% of the malignancies diagnosed in infants less than one year of age, 45% of malignancies in one to four year olds are leukaemias, in children from five to fourteen, leukaemias, CNS tumours and lymphomas make up 75% of malignancies, while in fifteen to nineteen year olds carcinomas and germ cell tumours predominate (32%) [2]. Although dependent on tumour type, overall the highest incidence of childhood cancer is in the under five years age group and is slightly higher in boys (55%) [7]. This age group is characterised by rapid cerebral and functional development and is therefore a period when the brain is particularly vulnerable to the pathological effects of disruption to sleep. There is also a second peak in incidence that occurs during puberty.

Sleep in childhood

Sleep is a major physiological drive which is essential for normal growth and development of both the body and the brain. During childhood, sleep is at a lifetime maximum, with children between the ages of two and five spending about half of each 24 h asleep [4].

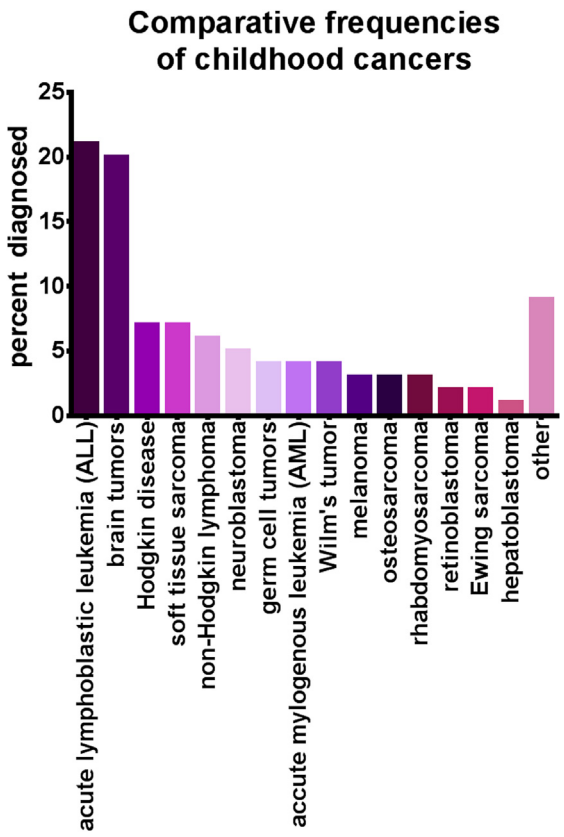

Fig. 1. Comparative frequencies of childhood cancers, represented as a percentage of the total number of childhood cancers diagnosed (n = 13,500). Adapted from: *Childhood Cancer Statistics*. CureSearch for Children's Cancer http://www.curesearch.org/Childhood-Cancer-Statistics/.

Sleep problems are common in children affecting 20–50% of otherwise healthy children [4]. Dysomnias and parasomnias are the most common sleep problem in children (up to 80% in preschool-aged children), followed by snoring, obstructive sleep apnoea and circadian rhythm disorders [4,8]. While the amount of sleep each child needs is to some extent dependent upon the individual, insufficient or poor quality sleep, impacts a child's mood, cognitive function, behaviour and the propensity for obesity (Table 1).

Sleep has also been shown to significantly affect a child's resilience, that is, the ability to recover normal functioning following stressful situations. The greater the sleep disturbance, the more resilience was reduced and increased problematic behaviour (both internalising and externalising), depression and anxiety were noted [9]. Therefore, maintaining a normal sleep pattern in situations of stress, such as those associated with cancer is of vital importance for improving a child's long-term QOL.

Fatigue and sleepiness

Although interrelated, fatigue and sleepiness are distinct phenomena. Sleepiness is a normal physiological state, and reflects an individual's propensity to sleep. Sleepiness becomes pathological when it becomes pervasive such as in narcolepsy or is reduced as in insomnia [10]. In contrast, fatigue relates to an overwhelming lack of energy and a feeling of exhaustion that is associated with impaired physical and/or cognitive function [10] but which does not lead to sleep. Fatigue can be either central or peripheral. Central fatigue originates in the areas of the brain related to mood, emotion and psychological arousal, and is associated with increased serotonin release [11]. Peripheral fatigue is related to mechanisms such as neuromuscular transmission and impulse propagation, dysfunction of the sarcoplasmic reticulum, and other metabolic factors that disrupt energy provision and muscle contraction [11]. There is scant knowledge of the impact of central versus peripheral fatigue in cancer patients, although a recent study reported that post-cancer fatigue in adults was not characterized by either high central muscle fatigue or low peripheral fatigue, suggesting a different underlying physiological mechanism to cancer-related fatigue compared with other fatigue syndromes [12]. The adverse effects of fatigue and sleep disorders on children with cancer are currently being under-rated by clinicians. Highlighting this, one study of 158 children receiving intravenous antineoplastic therapy identified that 80% of the children suffered from symptoms of fatigue and 41% from significantly severe sleep problems [13].

Table 1
Impact of insufficient or poor quality sleep.

Mood	Irritability
	Increased emotional lability
	Moodiness
	Depression
	Anxiety
Cognitive function	Inattention
	Poor concentration
	Impaired vigilance
	Decreased executive functioning
	Learning difficulties
	Poor academic performance
Behaviour	Overactivity
	Noncompliance
	Oppositional behaviour
	Poor impulse control
	Increased risk taking
Obesity	Reciprocal amplificatory effects on sleep quantity, sleep quality and obstructive sleep apnoea

Adapted from [4,10,11].

Clinical assessment of sleepiness and fatigue in children

To asses sleepiness subjectively the Epworth sleepiness scale (adapted for children), the Stanford sleepiness scale, and the paediatric daytime sleepiness scale, have been utilised in paediatric populations. The fatigue severity scale and the fatigue assessment instrument provide information to assess and monitor fatigue. Sleepiness can also be measured objectively. The most widely used and scientifically validated method is the multiple sleep latency test (MSLT). In this test a patient is given five opportunities to nap spaced evenly throughout the day under standardised conditions, with the result expressed as the average time taken to fall asleep across all the naps (mean sleep latency) [14]. Fatigue however, has no comparable objective measure, and yet is associated with significant morbidity in many conditions including cancer.

The effect of cancer on sleep

Cancer has a detrimental effect on sleep that may last from diagnosis, through the treatment phase and for many years into the future in cancer survivors, via disruption of the circadian, homeostatic, cardio-respiratory, neurologic and the behavioural mechanisms that are involved in the regulation of sleep [15]. Additionally, cancer amplifies any sleep problems that might be present prior to cancer diagnosis. Sleep problems are prevalent in cancer patients, reported in 25–59% of adult patients [16] and include difficulty falling or staying asleep, poor sleep quality and short sleep duration. These symptoms in cancer patients mirror the symptoms of chronic insomnia in the general population [17].

Excessive daytime sleepiness (EDS) is the most common symptom of a sleep disorder reported in children with cancer [18]. EDS may be the manifestation of insufficient night time sleep as a result of insomnia or disruption to the circadian rhythm. Additionally, it may result from sleep fragmentation due to anxiety, depression, sleep disordered breathing, movement disorders, parasomnias and environmental factors and/or an increase in the drive to sleep associated with increased intracranial pressure, chemotherapy, or secondary narcolepsy resulting from, for example, craniopharyngioma or astrocytoma affecting the pons or the hypothalamus [19]. Sleep disordered breathing may also contribute to EDS and may include obstructive sleep apnoea due to obesity or central sleep apnoea following involvement of the brainstem particularly the medulla. A retrospective study of 70 children diagnosed with cancer between 1994 and 2009, who were referred to a paediatric sleep clinic for evaluation of their sleep problems [18] included 25% who were still receiving treatment with the remainder having completed their cancer treatment. Sleep problems were often present in a combination of different symptoms however, the most common sleep problem reported was EDS. In this study, EDS was defined as daytime napping when napping had been previously discontinued, difficulty waking up in the morning, inability to remain awake during daytime activities such as during school and by either a mean sleep latency on MSLT of less than 15 min with sleep present on at least two of the five nap opportunities through the day, or by actigraphy showing consistent daytime sleep of longer than 30 min/d. The other sleep problems found in these children included insomnia, parasomnias, seizures during sleep, hypoxia, fatigue and circadian rhythm disorders [18].

Cancer can have either direct effects on sleep whereby the physical presence of a tumour causes brain injury, or indirect effects, including those due to treatment (especially steroids) stress, neurosurgery, hydrocephalus, chemotherapy, cranial radiation therapy, pain, fatigue, endocrinopathies or organ damage [15], as summarised in Fig. 2. Cancer also affects sleep by disrupting the normal circadian rhythm of the sleep–wake cycle.

Circadian rhythms are biological cycles of physiological and behavioural processes that are entrained on an approximately 24 h cycle by time cues known as zeitgebers such as bright light, and are controlled by the biological 'master' clock located in the suprachiasmatic nuclei of the hypothalamus [20]. The circadian rhythm times processes such as hormone release, body temperature, blood pressure and the sleep–wake cycle. Therefore, disruption to the circadian rhythm invariably leads to sleep problems [21]. Cancer and the circadian rhythm have a bidirectional relationship. Epidemiological studies have demonstrated that circadian rhythm disruption in adults increases the risk of breast, colon, prostate, lung, ovarian and hepatocellular carcinoma [22]. In the opposite direction, cancer and its treatment have been documented to cause circadian rhythm disorders [18]. The mechanism by which disruption to the circadian rhythm can lead to cancer has been well researched and documented in the literature (for review see Savvidis and Koutsilieris [23]). However in the opposite direction, the mechanism(s) by which cancer disrupts circadian rhythm remains unclear. Timing of the molecular clock in normal cells synchronises the cellular need for energy with food intake during the sleep–wake cycle. However, if cancer cells can disrupt these circadian oscillations and not have periods of cellular inactivity, then there is the potential for uninterrupted replication. One mechanism hypothesised to achieve this is via DNA methylation of specific clock genes, which not only impacts the peripheral circadian clocks but also the central 'master' circadian clock, potentially leading to sleep problems [24]. Furthermore, histone post-translational modifications and chromatin remodelling have been associated with regulating circadian clock gene expression in a number of conditions and syndromes in which disrupted sleep is symptomatic [24]. Whether the same mechanism is involved in the disruption to the circadian rhythm and consequent sleep disorders related to cancer, is yet to be elucidated.

Another mechanism proposed to account for the cancer-related alterations to the circadian rhythm, is via hypothalamic injury which leads to dysfunction of the hypothalamic-pituitary-adrenal axis and/or the suprachiasmatic nucleus. The suprachiasmatic nucleus signals the sleep and wake regulatory centres of the pre-optic and dorsomedial hypothalamus to regulate the 24 h sleep/wake cycle [25]. Evidence linking sleep disorders, cancer and the hypothalamic-pituitary-adrenal axis comes from adult studies that have reported flattened diurnal cortisol rhythms in women with breast cancer in comparison to healthy women who exhibited a normal, marked diurnal variation in cortisol [26]. Furthermore, the accumulated effects of psychological stressors, including perceived stress, lack of social support, poor sleep quality, pain, depression, and poor performance on explicit memory tasks, were associated with flattened diurnal cortisol rhythms in these women [26,27]. The loss of the normal cortisol nadir at bed time may have caused the associated sleep problems and further disruption to the circadian rhythm. Research conducted into the pathway by which cortisol production is reduced, suggested it was a result of an impaired central nervous system (CNS) drive reducing the hypothalamic output of corticotropin-releasing hormone causing decreased secretion of adrenocorticotropin hormone, and ultimately reduced cortisol production [28].

Additionally, the opposing effects of melatonin and serotonin levels, which are high and low at night respectively, are critical for the sleep/wake cycle [29]. Damage to the CNS which alters their synthesis, also impacts the sleep/wake cycle [29]. Therefore, cancers in general and especially cancers such as CNS neoplasms which can cause direct damage to the hypothalamus (particularly the suprachiasmatic nucleus) and the pineal gland have the potential to impact the normal circadian rhythm and induce sleep disorders.

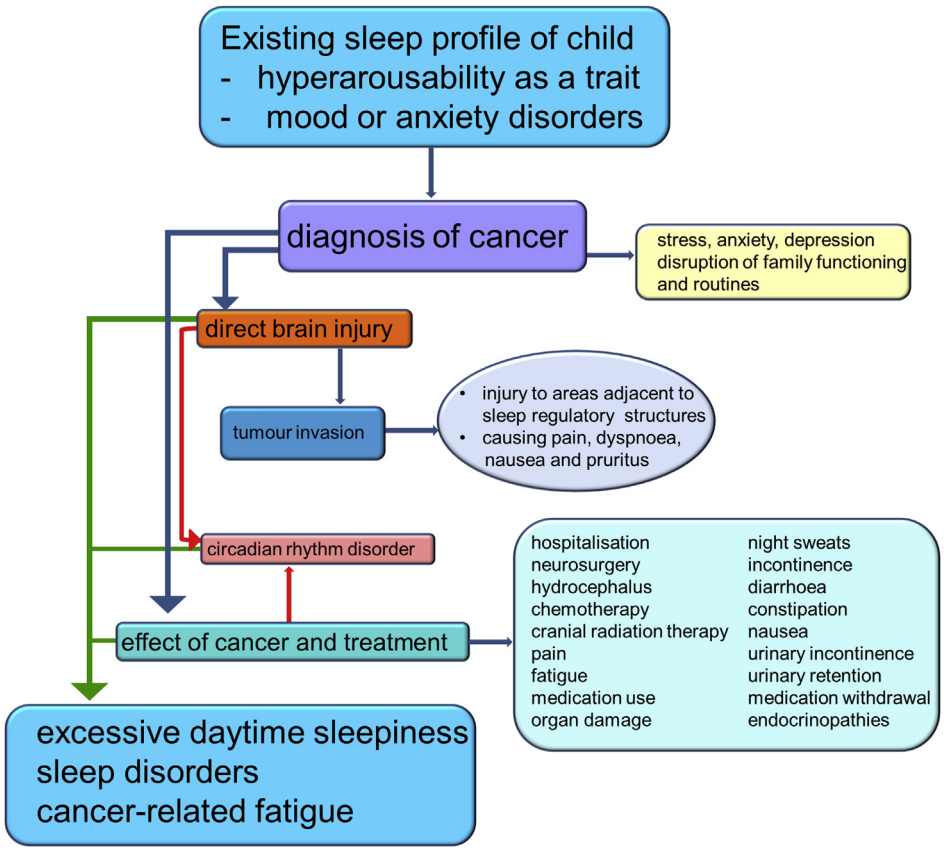

Fig. 2. The causes of sleep problems in children diagnosed with cancer.

The effect of pain on sleep in children with cancer

Pain affects the quality of sleep [30] and conversely, sleep affects the perception of, and tolerance to, pain [31]. Pain and sleep share common afferent circuits including the parabrachial-amygdala and the parabrachial-hypothalamic pathways [32,33], which may explain how both pain and sleep disturbances may generate cognitive, affective and motivational dysfunctions that can promote hypervigilance and frequent awakenings [46,47]. Pain is felt by 59% of adult cancer patients during treatment and by 64% with advanced disease [34]. While children with cancer report varying types and degrees of pain, from acute, procedure-related pain to progressive chronic pain associated with the progression of the disease or sequelae of treatment, pain is most commonly a problem during the early phase of treatment [35,36]. A longitudinal study of 95 children (4–17 y) with ALL was conducted to investigate the pain experience in the first year of treatment [37]. The potential sources of pain included the disease process, side effects of the chemotherapy (leg pain, abdominal pain from the medications and/or repeated vomiting and headache), or lumbar puncture (headache) and bone-marrow aspiration. Analgesia was the most commonly used pain management strategy, however, distraction techniques such as watching TV, resting, heat or cold packs, massaging, rubbing or stretching the painful area and receiving social support (usually from parents) were also successful. This study however, highlights the importance of good pain management in the care of children with cancer.

Opioids are often used as treatment for pain in children with cancer and can have a profound effect on sleep [38]. Endogenous opioids are believed to be important in the onset and maintenance of sleep and therefore in arousal and awakening. Although the mechanism of action of opioids on sleep remains unclear, it has been hypothesised to involve the neurohormone vasopressin via a circadian mechanism driven by the suprachiasmatic nuclei [38,39]. Exogenous opioids bind to the same receptors as the endogenous peptides and both acute and chronic use has an effect on sleep architecture indicated by a reduction in rapid eye movement sleep [40]. The alternate use of semi-synthetic, partial opioid-receptor agonists such as buprenorphine, which although 25–30 times more effective than morphine, leads to less dependence, tolerance and withdrawal symptoms than morphine are becoming more widely accepted [41]. Due to the close relationship between pain and sleep, effective clinical management of both are vital for maintaining good QOL for children with cancer throughout diagnosis, treatment and during the following years. The relationship between changes in sleep pattern and the stages of palliation has not been studied in children and is a further area for future research.

Sleep in children with cancer of the brain and central nervous system (CNS)

Of all of the cancers, malignancies of the brain and CNS most directly impact sleep. Tumour invasion of surrounding brain tissue results in pain and nausea [5]. Sleep problems invariably occur when specific areas of the brain are damaged by tumours of the CNS, especially the hypothalamic/pituitary region or areas in the immediate vicinity of sleep regulating structures in the diencephalon [18,42–44]. As with cancer overall, EDS is the most common symptom of a sleep disorder in children with brain tumours, which are the second most common cause of secondary narcolepsy [18,45]. Rosen and colleagues [18] identified that the children with

cancer most commonly referred to the sleep clinic for investigation of a sleep disorder, were those with neoplasms of the CNS involving the hypothalamus, thalamus and brainstem, and these children also had the most frequent and severe sleep problems. While EDS was reported overall in 60% of the children with cancer, it increased to 80% of the children with CNS neoplasms.

Treatment of brain tumours also impacts upon the sleep of these children. Ten children, who had been treated for craniopharyngiomas, underwent overnight polysomnography and MSLTs, 1.5–16.1 y postoperatively. Compared to 18 healthy children, the children with cancer had severely disturbed sleep, with more awakenings and for longer periods of time, although the regulation of the ultradian sleep rhythm was found to be normal [46]. In contrast, a study by Greenfeld et al., [47] of 40 children (mean age 9.9 y) diagnosed and treated for CNS tumours (mean time from diagnosis to participation was 4.1 ± 1.4 y), and 61 age-matched, healthy controls (mean age 11.4 y) found no significant sleep disturbances in the children with cancer. The difference between these two studies likely relates to the type of brain tumour, as 50% of the children in the latter study had posterior fossa tumours, 25% midbrain tumours, 15% frontal and others 2%. These tumours are less likely than craniopharyngiomas to have a direct effect on sleep processes due to their location in the brain. However, while craniopharyngionmas are very rare and treated surgically rather than with chemotherapy or radiation, medulloblastoma is the most common paediatric brain tumour and surgery in conjunction with posterior fossa syndrome causes sleep disruption. i.e., it is related to the trauma of surgery and further compounded by the other factors as already noted such as steroids, antinausea drugs, etc. The latter study did find a difference using the actigraphy data, with the cancer group having an overall increase in total sleep time, which the authors suggested might be indicative of a mild manifestation of EDS in the children with cancer.

A cross-sectional study compared 31 CNS tumour patients (mean age 11.8 y) to 78 children treated for a non-CNS malignancy, with both groups having completed treatment more than six months previously [48]. The children had widely varying tumour types, combinations of treatment including surgery, chemotherapy and/or radiotherapy, and medication usage. They compared sleep, fatigue and psychosocial functioning and found that increased somnolence was reported in children with CNS tumours compared with the children with a non-CNS malignancy and their increased sleepiness correlated with lower fatigue related QOL and worse psychosocial functioning. This lead the authors to suggest that further investigation should focus on improving sleep quality and reducing fatigue in children with CNS tumours.

A retrospective analysis of 28 children (median age at diagnosis, 8 y; median time of follow-up 9 y) with craniopharyngioma, aimed to identify clinical factors influencing the development of daytime sleepiness and sleep disorders, including extent of resection, treatment modalities and endocrine status, sleep questionnaire and sleep study results [49]. Nineteen of the children reported daytime fatigue or sleep disturbance. The study found that while the extent of the surgical resection did not increase the risk of the patient-reported daytime sleepiness or of a sleep disorder, more frequent radiation therapy resulted in more daytime sleepiness and dysfunctional sleep. The authors recommended that formal sleep evaluations be performed on all children with craniopharyngioma, as these children are at an increased risk of being overweight or obese and therefore are at an increased risk of developing obstructive sleep apnoea.

Cranial radiation therapy is very effective in the treatment of many CNS neoplasms, especially in instances where surgery is not indicated such as germinoma. However, cranial radiation can be damaging to the developing brain and is not commonly used in children under five and then only with a reduced dosage or limited field, or with stereotactic field radiotherapy [50,51]. Newer protocols with conformal radiation to the primary site reduce overall doses to the craniospinal irradiation axis, but cranial radiation therapy remains a potential cause of injury to the hypothalamus and pituitary gland with impacts on sleep. The cyclic production of growth hormone, prolactin and leptin, have been associated with the sleep/wake cycle [52–54] and dysfunction in the production of these hormones has been reported in patients following cranial radiation therapy [55,56]. Decreased leptin has been associated with an increased risk of metabolic syndrome and obesity which compounds fatigue and sleep disturbance, particularly in long term survivors [57].

Children undergoing cranial radiation therapy commonly suffer from somnolence syndrome, which includes a range of symptoms from mild drowsiness to marked lethargy accompanied by prolonged periods of sleepiness, irritability, anorexia, nausea, vomiting cerebellar ataxia, dysarthria, dysphasia, low grade fever and headache [58]. While somnolence syndrome commonly occurs four to six weeks following cranial radiation therapy, the incidence can be reduced with steroid administration and the effects are transitory [58]. To investigate whether cranial radiation therapy had long-term effects on sleep, 25 adults diagnosed with either medulloblastoma ($n = 17$) or other intracranial tumours ($n = 8$) during childhood were assessed 8–29 y following treatment and compared with a healthy, age-matched control group [57]. The serum growth hormone peak during insulin-induced hypoglycaemia and serum concentrations of prolactin and leptin were analysed. Sleep and circadian rhythm were assessed by questionnaires and by actigraphy to evaluate the occurrence of disturbed sleep, the ability to overcome drowsiness and the sleep/wake cycles. The adults in the cranial radiation therapy group had significantly longer sleep duration, less sleep fragmentation and lower tolerance for alterations to the timing of sleep, compared with the control group. The negative predictors of sleep changes determined by regression analysis were radiation dosage and neuroendocrine status, suggesting that some of the alterations to the sleep/wake rhythm seen acutely may be normalised with hormonal supplementation.

Indirect sleep disorders also occur as a consequence of brain tumours in children when the tumour results in injury to either the respiratory control centre of the medulla leading to central sleep apnoea, or to the glossopharyngeal, vagus and hypoglossal nerves innervating the pharyngeal dilator muscles, leading to obstructive sleep apnoea [15,59]. Both central and obstructive sleep apnoea cause sleep disruption and fragmentation [60,61]. Rosen et al. [18], reported that sleep disordered breathing (SDB) was diagnosed in 40% of the total number of children with cancer, which rose to 46% of the children with neoplasms of the CNS. Children with neoplasms of the CNS also commonly had more than one sleep problem, usually both EDS and SDB. A further study of 31 CNS tumour survivors who were referred for assessment of sleep disorders, on average 6.9 y following tumour diagnosis (mean age at diagnosis was 7.4 y), identified that EDS remained the most common reason for referral [59]. Of the sleep disorders diagnosed, obstructive sleep apnoea was the most common (14 children), followed by central sleep apnoea (four children), hypersomnia (four children) and narcolepsy (three children). Twenty-six of the children were obese or overweight, 17 had tumours located in the suprasellar (sellar/parasellar/hypothalamic) region and radiation therapy was the most common treatment. The study concluded that those children who had been diagnosed with suprasellar tumours and co-morbid overweight or obesity, were more likely to complain of EDS and be at higher risk for obstructive sleep apnoea.

Sleep in children with leukaemia

Sleep disorders associated with leukaemia are associated more with the treatment of the cancer rather than a direct insult of the cancer. Sleep disturbances, pain and fatigue are problematic in children with leukaemia. Following diagnosis, children with ALL are treated with a regime of six to eight months of intensive chemotherapy that can be followed by a further two years of maintenance chemotherapy [62]. Dexamethasone has marked antileukaemic effects and as such has become a widely used chemotherapy agent in the treatment of ALL [63], albeit having serious side effects such as sleep disorders, fatigue, psychosis and mania [64,65].

To determine the effect of dexamethasone on sleep, 100 children with ALL (5–18 y) wore an actigraph to monitor sleep/wake patterns during two consecutive five-day periods [64]. The children received dexamethasone only during the second period. The total time asleep at night and during naps increased as did fatigue, during the dexamethasone treatment. In addition, the parents reported the number of night time awakenings, restless sleep and nap times, significantly increased during dexamethasone treatment. A further study, which although being a multi-centre study only had a small cohort ($n = 17$), determined that impaired sleep may be a determinant in the poor QOL found in children (2–18 y) with ALL halfway through maintenance treatment with dexamethasone [66]. In contrast to the previous study, this study did not identify that dexamethasone treatment worsened sleep quality or QOL compared to periods without dexamethasone treatment. However, the authors did acknowledge the small size of the study and the need for more extensive investigation.

Gedaly-Duff et al. [62], conducted a pilot study over three days of nine children (8–16 y) diagnosed with ALL who were being treated with vincristine during the maintenance phase of their treatment. Pain was self-rated by the children morning and night, sleep was assessed by actigraphy and fatigue by questionnaire. The children reported pain, fatigue and sleep disturbances similar to that reported in the literature for other cancers. A similar, but more extensive study by Zupanec and colleagues, of 64 children (4–18 y) also receiving maintenance chemotherapy for ALL investigated sleep habits and fatigue using questionnaires completed during a week when dexamethasone was not being administered [67]. Eighty-seven percent of children reported sleep disturbance which was positively correlated with fatigue scores. Answers from open-ended questions regarding the sleep habits of these children since they were diagnosed, resulted in a number of common themes. These included disturbed sleep and changed sleep habits, with parents reporting that medication, especially dexamethasone, and the schedule of medications prevented the children sleeping well and that sleeping with someone, comforting activities or routines, medications, food and drink helped the children to get to sleep at night. In contrast, some reported unchanged or even improved sleep. Both the Zupanec et al. [67] and the Gedaly-Duff et al. [62] studies also questioned the parents of the children participating in the study regarding their own sleep quality. Results indicated that parents also had significant sleep disturbance although interestingly in the Gedaly-Duff et al. [62] study, the parents significantly underestimated their sleep disturbance by self-reported questionnaire compared to that obtained by actigraphy. These studies suggest that improving sleep quality in children during treatment for ALL, and that of their parents, may improve health outcomes for both.

The mechanisms by which dexamethasone disturbs sleep and causes fatigue was investigated during a ten day study of 100 children (5–18 y) diagnosed with low or standard-risk ALL receiving dexamethasone treatment [68]. Disrupted sleep was most significantly related to the ALL risk group. Neither fatigue nor disrupted sleep, were associated with serum albumin levels, however candidate genes were identified that may explain the disrupted sleep and increased fatigue associated with dexamethasone treatment.

Fatigue in children with cancer

Similar to sleep disorders, fatigue can affect both children and adults with cancer from diagnosis, during treatment and throughout the following years in cancer survivors. Although well recognised as a problem in adults, cancer-related fatigue has only received limited clinical recognition by paediatric oncologists until the last decade. The reason for this may be because of the aggressive treatment that paediatric cancer patients receive, which is focussed through necessity on cure. Therefore, side effects such as fatigue may have been viewed as an unavoidable side-effect [69]. However, similar to adults, children have reported fatigue to be the most distressing of their treatment-related symptoms [70].

The commonality of symptoms between sleep disorders and fatigue in cancer patients has led to the speculation that they share a common physiological pathway. Cancer-related fatigue occurs concurrently with disrupted sleep patterns and it is hypothesised that there is a strong, perhaps reciprocal relationship between the two [28]. The relationship was identified in studies of adults with cancer with actigraphy, demonstrating that patients experiencing restless sleep at night also experienced more intense daytime fatigue, increased daytime napping and were less active [71]. Patients reporting cancer-related fatigue also had significantly longer sleep latency and more frequent and longer-lasting periods of wakefulness during the night compared with non-fatigued patients [72].

In one study aimed at defining cancer-related fatigue in children, 29 children receiving treatment for cancer were grouped into either a 7–12 y or a 13–16 y old group [73]. The younger group described fatigue as a profound sense of being physically tired or having difficulty opening their eyes or using their arms or legs. The adolescents described fatigue as a changing state of exhaustion including physical, mental, and emotional tiredness. Since this study describing fatigue in paediatric cancer patients, a limited number of studies have investigated cancer-related fatigue in children, usually either in combination with sleep disorders or as one aspect of a QOL study [64,74–80]. Hockenberry et al., [76] attributed the lack of clinical interest in cancer-related fatigue in children, in part to the absence of reliable and valid measures of evaluation. Consequently, they developed the childhood fatigue scale, a 14 part Likert scale questionnaire for 7–12 y old children. Hockenberry et al., also developed two further questionnaires to be completed concurrently with the childhood fatigue scale, one for parents regarding their perception of their child's fatigue, and another regarding nursing staff's perception of the child's fatigue [76]. A similar questionnaire was validated a few years later for adolescents with cancer (13–18 y), the fatigue scale-adolescents [75].

The childhood fatigue scale was used to assess fatigue in 40 children (7–12 y) being treated for cancer, including chemotherapy and/or radiotherapy [78]. Children diagnosed with brain tumours were excluded. The children's fatigue levels were significantly increased during treatment, and the medical procedures and the hospital environment were identified as the major causative factors involved. The same research group expanded this cohort in a later study, to include 29 13 to 15 y old adolescents with identical inclusion and exclusion criteria [79]. A parent from both age groups was also included in the study to provide the parental perspective of the child's fatigue. Again, adolescents and parents reported a significant increase in fatigue during treatment and similar to the previous study, the medical procedures and the hospital environment were identified as the major causative factors involved.

A different approach was taken by Yeh et al., [80] who investigated fatigue in children (7–18 y) receiving chemotherapy treatment without concomitant radiotherapy and who had not undergone a bone marrow transplantation, in relation to clinical factors including haemoglobin value, type of chemotherapy agents prescribed and corticosteroid use. Fatigue was assessed by both self-report and parental report. The children in this study had more fatigue during the first few days of a new cycle of chemotherapy. Fatigue was significantly associated with corticosteroid use and their haemoglobin value, and was sustained for several days reaching a maximum on the fifth day of treatment. This study suggests that lower haemoglobin levels contribute significantly to fatigue. However as the study also identified that the level of fatigue varied over the course of time and treatment, the authors suggest that frequent checks of haemoglobin levels might increase the oncologist's understanding of the fatigue that occurs as a result of treatment. It is important to note that to date there are no studies that investigate specific haemoglobin correction interventions. Changes in fatigue that occurred over time during treatment were not determined to be associated with the type of chemotherapy agent used.

Cancer-related fatigue has recently received more attention with recommendations published from the National Cancer Institute Clinical Trials Planning Meeting and a National Cancer Institute working group that high-priority research and clinical trials be conducted in both adults and children over the next several years [81]. The recommendations focus on advancing understanding of the biobehavioural mechanisms of cancer-related fatigue, identifying new targets for intervention to prevent or treat cancer-related fatigue, pooling and comparing data across studies and dissemination of the efficacious interventions into the community. Successful implementation of these recommendations has the potential to not only advance our knowledge, but also to improve clinical management of cancer-related fatigue.

Symptom clustering

The term symptom clustering describes two or more symptoms that are related to each other and occur together [82]. To date scant research has been performed on the concept of symptom clustering in children with cancer. The clustering of symptoms can affect the clinical outcome as the symptoms that comprise the cluster may have a multiplicative effect. A proposed symptom cluster of fatigue, sleep disturbance, nausea and vomiting was examined in 67 children (7–18 y) who were receiving chemotherapy with cisplatin, doxorubicin or ifosfamide [77]. The cluster of increased fatigue and sleep disturbance in adolescents was associated with more depressive symptoms and changes in behaviour, whereas fatigue alone increased depressive symptoms in the children. Furthermore, when parents perceived their children or adolescents being more fatigued, they reported more emotional and behavioural issues. More research is needed on the role symptom clustering plays on the health status of children and adolescents during treatment of childhood cancer to improve the care of these young individuals.

Hospitalisation, sleep and fatigue in children with cancer

Children with cancer are admitted to hospital for a variety of reasons, including chemotherapy, the management of neutropenia, fever, or side-effects of treatment, and for end-of-life care. The hospital environment adds a further dimension to sleep disturbance in children with cancer. There are numerous causes of sleep disruption in a hospital environment that have been identified (Fig. 3) and the effects of the sleep disruption can last from one to seven weeks after discharge, even for a short stay in hospital in young children [83]. Whilst in hospital for chemotherapy, children and adolescents can be woken up to eight times more than healthy children in the home environment [84]. The hospital environment is one of relatively high levels of sound and light intensities, some of which is necessary for patient care. The sound, light and temperature were measured in the hospital rooms of 15 school-aged children receiving chemotherapy as inpatients [85]. This study identified that within the hospital rooms, there were persistently elevated sound levels accompanied by abrupt increases in intensity throughout the night, up to ten times greater than that of a healthy sleep environment and at a level recognised as being disruptive to sleep [85]. These findings highlight the need for hospitals to

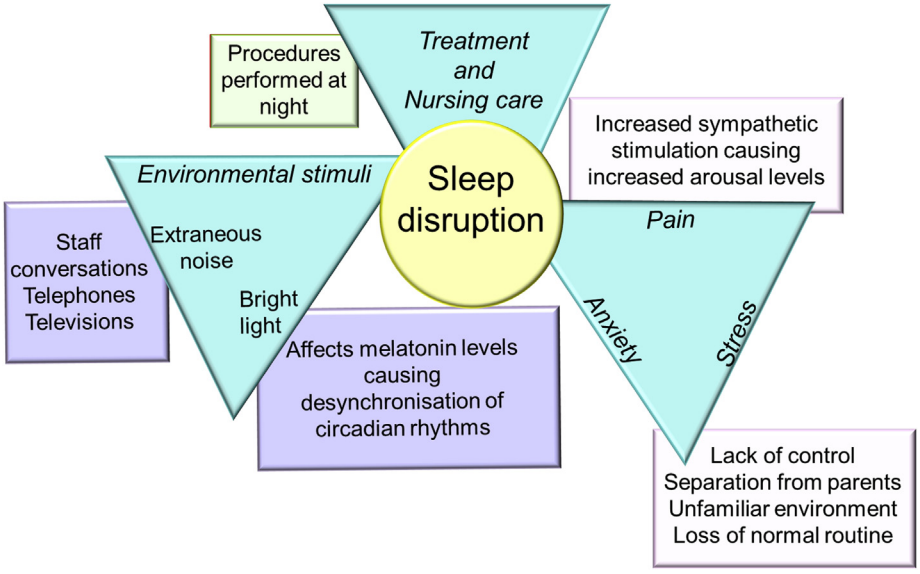

Fig. 3. Causes of sleep disruption in the hospital environment for children with cancer.

minimise the noise intensity that can affect the sleep quality of hospitalised children.

As in the home environment, fatigue is a common complaint from hospitalised children and adolescents with cancer. Fatigue has been attributed to altered sleep patterns and factors associated with treatment such as medication and disrupted sleep [73]. A pilot study was conducted on 29 patients (7–8 y) hospitalised for chemotherapy who undertook enhanced physical activity therapy for 30 min twice daily for two to four days [86]. Fatigue was assessed using an age-appropriate questionnaire, the fatigue scale, and sleep using actigraphy and a sleep diary. Sleep efficiency was found to be significantly improved in the participants who were exercising compared with a control group who did not exercise. This study lays the groundwork for future studies to investigate the effect of physical activity on sleep in children with cancer.

Treatment of sleep disturbances and fatigue in children with cancer

There is scant adult or paediatric literature on the interventions that have been tried to reduce the effects of cancer on sleep disturbances and fatigue. Orsey et al., [87] examined the relationship between sleep and physical activity in 36 children (8–18 y), undergoing treatment for their cancer (23 leukaemia/lymphoma, five brain tumour and eight solid tumour). Sleep was measured using actigraphy and sleep diary, and physical activity by actigraphy, over seven days. Study data were compared with normative data compiled from multiple studies of over 1700 healthy 1–18 y old children and adolescents. The results demonstrated that the participants had impaired sleep with decreased total sleep time, increased wake after sleep onset, increased arousals and decreased sleep efficiency compared with the normative values. Higher average activity was identified as being associated with improved sleep quality and sleep efficiency. Similar to the hospital intervention study [86] outlined previously, Orsey and colleagues [87] also suggested that physical activity may have beneficial effects on sleep in paediatric oncology patients, indeed a number of studies have evaluated exercise programs in oncology patients although not many have included sleep as an outcome measure.

A systematic review of 17 studies of clinical exercise intervention in paediatric oncology patients [88] reported that such interventions are feasible and safe, especially in the case of children with ALL and during treatment [88]. While no adverse effects were reported, the positive effects of exercise included improvement in the levels of fatigue, improved sleep (sleep efficiency and sleep duration), increased strength and improved QOL. Positive effects were also identified on the immune system, body composition, overall activity levels and specific aspects of physical function. However, the authors caution that future research which focuses on child-specific methodology and requirements is needed prior to the establishment of exercise recommendations for children with cancer.

Further behavioural modification interventions such as mindfulness-based meditation are also being trialled. An on-going trial is investigating the effects of mindfulness-based meditation on QOL, sleep and mood in adolescents (11–18 y) with cancer and a control group [89]. The intervention will comprise eight weekly sessions, lasting 90 min each, following which the potential benefits of this intervention on both the psychological and physical health of the adolescents with cancer will be assessed.

Parents and/or caregivers of children with cancer also recognise the impact of cancer on the children's sleep and actively intervene to improve the situation. One study detailed the efforts made by 35 caregivers of children (mean age 7.9 y SD 4.8 y) receiving treatment for cancer, to prevent and treat their child's sleep problems [90]. Their efforts focussed on practicing good sleep habits in a safe, secure and comfortable sleep environment. Maintaining a bedtime routine and relaxing activities including reading prior to bed were commonly cited by the caregivers. Additional strategies included both non-pharmacological interventions, such as warm lavender/Epsom salts baths for relaxation, and warm milk before bed, and pharmacological interventions, such as pain and anti-nausea medication. A comparatively recent pharmacological strategy to improve sleep in a number of varied situations, including cancer, is the use of exogenous melatonin.

Melatonin is an endogenous indoleamine which is not only an effective antioxidant and free radical scavenger, but is also one of the primary circadian pacemakers [91]. Although melatonin is an 'over-the-counter' drug and widely available in many countries for treatment of sleep disorders, there have been no double-blind, placebo-controlled studies undertaken to date, in either adults or children with cancer, to investigate the use of melatonin to treat sleep issues in these populations. Decreased melatonin synthesis has been demonstrated in children with cancer. A study of 79 children with either craniopharyngioma or hypothalamic pilocytic astrocytoma, identified an association between decreased nocturnal melatonin levels and daytime sleepiness [92]. A subsequent study by the same group firstly confirmed their previous findings in a new cohort of 79 paediatric craniopharyngioma patients, 19 with hypothalamic pilocytic astrocytoma and 30 controls, and secondly investigated the effects of melatonin administration on ten adult obese patients, who had childhood craniopharyngioma [93]. Melatonin treatment consisted of daily oral doses of 6 mg taken in the evening before bed. The degree of daytime sleepiness was significantly improved following melatonin use although no details of the time period of melatonin administration were provided for the study. As with physical activity intervention strategies, the use of melatonin to treat sleep disorders in children with cancer requires much more extensive research.

There are numerous drugs approved for the treatment of insomnia but none have been tested for efficacy or safety in adults or children with cancer. In fact, the use of tranquilizers and sleeping pills (drug names not provided) has been associated with increased severity of symptoms such as insomnia, fatigue, pain, dyspnoea and constipation, which lead to a poorer QOL in 900 adult cancer patients [94]. Another strategy is to combat daytime sleepiness using daytime medications such as stimulants.

Methylphenidate has been administered over recent years for the treatment of cancer-related fatigue, however there are few studies to validate its efficacy and safety in cancer populations. Methylphenidate is most commonly prescribed for the treatment of attention deficit hyperactivity disorder and is a psychostimulant which increases the dopamine levels in the CNS. A recent systematic review and meta-analysis concluded that the existing trials of methylphenidate for the treatment of cancer-related fatigue in adults provided only limited evidence supporting its use and further studies are needed before recommendation on their usage and safety can be made [95]. The single study that has been conducted in childhood cancer survivors, investigated the effect of methylphenidate use on the growth patterns of the children compared to case-matched childhood cancer survivors who were not administered methylphenidate [96]. The focus of this study was the use of methylphenidate to treat attention deficit hyperactivity disorder in these children 12 mo following completion of treatment, rather than any associated cancer-related fatigue. However, this study does give some indication of the safety of using this drug in children following cancer treatment. The authors reported that the children taking methylphenidate experienced modest but significant reduction of body mass index (BMI)

and weight, but not height, across the first year of methylphenidate use, suggesting it is reasonably well tolerated. The authors caution though that clinicians should balance the intended benefits of methylphenidate use with the potential effects on growth. Methylphenidate is also associated with other side-effects including appetite suppression, hypertension and insomnia [97], so there is an urgent need for trials to assess whether the benefit for treating cancer-related fatigue in children outweighs the risks involved. Newer non-amphetamine alerting agents such as modafinil have been shown to be successful and safe in reducing daytime sleepiness in children with narcolepsy but to date no studies have been published on modafinil's efficacy and safety in children with cancer [98].

Long-term implications of surviving childhood cancer on sleep and fatigue

In adult cancer, fatigue and sleep disorders have been reported by survivors of various types of cancer, months to years following treatment [99,100]. As the survival rate of childhood cancer increases, reports of ongoing sleep disorders and fatigue during the years following treatment and into adulthood, are also emerging in this population. The sleep problems initiated early in the diagnosis and treatment of cancers have the potential to become chronic via perpetuation of behaviours that have developed to compensate for sleep loss during illness, including daytime napping, bed sharing with parents, spending lengthy periods of time in bed without sleeping, and going to bed earlier and/or getting up later [101]. These behaviours contribute to poor sleep-related habits and dysregulation of the sleep–wake cycle, resulting in the difficulties in falling asleep and staying asleep overnight.

In one study carried out 3 y following completion of treatment for ALL, 62 children (5–17 y) from The Netherlands, were asked to complete questionnaires evaluating sleep, fatigue, depression and QOL [102]. Parents rated children as having more disturbed sleep, more fatigue and poorer QOL compared to the Dutch norm. However the children themselves reported less sleep problems, less fatigue and a better QOL compared with the Dutch norm. This study also identified that more sleep disturbance and fatigue correlated with more depressive symptoms and a worse QOL. The authors account for the discrepancy between parental and self-report as being the product of heightened parental anxiety and/or the adaptability of the children.

A large, multicentre epidemiologic study known as the Childhood Cancer Survivor Study (CCSS), was initiated to investigate adult survivors of a range of childhood and adolescent cancers. Mulrooney et al. [43] used data from the CCSS study of 1897 cancer survivors and 369 siblings to investigate the prevalence of, and risk factors associated with, fatigue and sleep disturbance in adult survivors of childhood cancer. The age at diagnosis of the participants ranged from less than 1 y to over 15 y and at follow-up from 18 y to over 50 y. Even 15 to 30 y after treatment, the cancer survivors had significantly higher scores for fatigue, sleep disorder and daytime sleepiness compared with the siblings group.

Cancer, sleep and neurocognition and behaviour

There have been numerous studies in children that have reported the association between cancer treatment and neurocognitive impairment (for review see Butler and Haser [103]). However, the role that sleep disruption plays in this has not been addressed. Irrespective of cause, sleep disruption results in detrimental effects on a child's neurocognition and behaviour [4]. For example, school-aged children with poor sleep quality due to conditions such as sleep disordered breathing have neurocognitive [104,105] and behavioural [106] deficits irrespective of the severity of the disease. These effects seem to be age dependent as, preschool-aged children with sleep disordered breathing exhibit only behavioural problems and have normal neurocognition [107]. Following treatment of sleep disordered breathing in school-aged children, any improvement in sleep disordered breathing severity is concomitant with an improvement in some areas of neurocognition, but not academic ability or behaviour [108]. It could be postulated that the earlier the cause of the sleep disruption is mitigated, the better the neurocognitive outcomes would be. To date, studies have not been performed to separate the effects of cancer-related sleep disruption and the direct effects of the treatment regime on neurocognitive dysfunction and behaviour in children with cancer.

In a study investigating neurocognition in long-term survivors of childhood cancer, Clanton et al. [3] analysed data from the CCSS and found that the neurocognitive function in this cohort was vulnerable to the effects of fatigue and sleep disruption, independent of the effects of cranial radiation therapy, steroids and antimetabolite chemotherapy, sex, and current age. The authors suggested that the importance of sleep hygiene should be emphasised to these survivors, as neurocognitive outcomes may be improved with improved sleep. In another study investigating neurocognitive outcomes in long-term survivors of childhood ALL (mean age 33 y; mean time since diagnosis, 26 y) impairment rates across neurocognitive domains ranged from 28.6% to 58.9% and were associated with reduced educational attainment and unemployment [109]. These studies highlight that cancer during childhood can have long-term effects on neurocognition. Further research is needed to elucidate whether interventions aimed at improving sleep quality in children with cancer will improve their neurocognitive and behavioural outcomes and thereby improve their long-term QOL.

Conclusions

The goal of cancer treatment is incontrovertibly the saving of life, however concomitant with the success of treatment comes an awareness of high rates of long-term sleep problems in children affected by cancer. Insufficient sleep quantity and reduced sleep quality are commonly reported by children beginning at the point of diagnosis, continuing during treatment and throughout the following years, sometimes even into adulthood. Sleep forms the bedrock of health-related QOL and good sleep is especially important for children with cancer, if they are to maintain the best possible QOL in a situation where they often have to cope with stress, anxiety, pain, illness and depression. Current research investigating the prevention and treatment of sleep disorders and fatigue in children with cancer is sadly lacking. Further research is required to establish the nature of the sleep disorders and the extent of fatigue related to specific malignancies and treatment regimes in children, so that treatments targeted at defined and specific problems in each patient can be instigated. Until such research elucidates the nature of defined problems for specific cancers, the recognition and treatment of sleep disorders and fatigue in children with cancer will remain poor. Younger children with cancer, preschool and early school-age, are an especially under-researched group, and yet are arguably the most vulnerable when it comes to the detrimental effects of sleep disruption and fatigue on their physical and neurocognitive development. Recognition and treatment of sleep disorders and fatigue in this population of children with cancer is vital before the problems become habitual and entrenched into their sleep behaviour. Future research is fundamental to improving the QOL in affected children.

Practice points

Improving the quality of sleep in children with cancer in the medium to long term may have the following effects:

1). Improve their quality of life;
2). Reduce fatigue and daytime sleepiness;
3). Improve neurocognition and reduce learning difficulties;
4). Improve their capability in dealing with the residual effects of the cancer such as depression, anxiety, pain and functional impairment.

Research agenda

Further research is required in the following areas:

1). More detailed information about the link between cancer-related fatigue and sleep problems in children undergoing treatment for cancer;
2). Better understanding of the risk factors and potential preventative factors for development of sleep problems during and after cancer treatment;
3). Randomised controlled trials investigating sleep interventions on fatigue, sleep and school performance in long term cancer survivors.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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